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Risk of oesophageal cancer among patients previously hospitalised with eating disorder

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ABSTRACT

Background: It has been suggested that the risk of oesophageal adenocarcinoma might be increased in patients with a history of eating disorders due to acidic damage to oesophageal mucosa caused by self-induced vomiting practiced as a method of weight control. Eating disorders have also been associated with risk factors for squamous cell carcinoma of the oesophagus, including alcohol use disorders, as well as smoking and nutritional deficiencies, which have been associated with both main sub-types of oesophageal cancer. There have been several case reports of oesophageal cancer (both main sub-types) arising in patients with a history of eating disorders.

Methods: We used linked records of hospitalisation, cancer registration and mortality in Scotland spanning 1981–2012 to investigate the risk of oesophageal cancer among patients with a prior history of hospitalisation with eating disorder. The cohort was restricted to patients aged ≥10 years and <60 years at the date of first admission with eating disorder. Disregarding the first year of follow-up, we calculated indirectly standardised incidence ratios using the general population as the reference group to generate expected numbers of cases (based on age-, sex-, socio-economic deprivation category-, and calendar period-specific rates of disease).

Results: After exclusions, the cohort consisted of 3617 individuals contributing 52,455 person-years at risk. The median duration of follow-up was 13.9 years. Seven oesophageal cancers were identified, as compared with 1.14 expected, yielding a standardised incidence ratio of 6.1 (95% confidence interval: 2.5–12.6). All were squamous cell carcinomas arising in females with a prior history of anorexia nervosa.

Conclusions: Patients hospitalised previously with eating disorders are at increased risk of developing oesophageal cancer. Confounding by established risk factors (alcohol, smoking, and nutritional deficiency) seems a more likely explanation than acidic damage through self-induced vomiting because none of the incident cases of oesophageal cancer were adenocarcinomas, and because the study cohort had higher than background rates of hospitalisation with alcohol-related conditions and chronic obstructive pulmonary disease.

1. Introduction

It has been suggested that the risk of oesophageal cancer, particularly adenocarcinoma, might be increased in patients with a history of bulimia due to acidic damage to oesophageal mucosa caused by self-induced vomiting practiced as a method of weight control [1]. Estimates of the prevalence of self-induced vomiting among patients with eating disorders vary according to the population studied, but perhaps also because of a reliance on self-reporting. Some of the highest estimates have emerged from an international study of eating disorders in families, which reported a prevalence of regular self-induced vomiting of 97% in purging bulimia nervosa, 94% in anorexia nervosa and bulimia nervosa, 73% in purging anorexia nervosa, 66% in bingeing anorexia nervosa, and 56% in eating disorders not otherwise specified [2].

Eating disorders have also been associated with smoking [3] and alcohol use disorders [4,5] in some studies. Smoking has been associated with both main sub-types of oesophageal cancer, and alcohol with oesophageal squamous cell carcinoma [6]. In the context of eating disorders, risk factors for oesophageal cancer may

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occur against a background of chronic nutritional deficiency [7], itself a probable risk factor for oesophageal cancer [6].

Oesophagitis has been reported in some patients with bulimia [8]. In addition, there have been at least six case reports describing seven patients with a prior history of bulimia [9–13] or psychogenic vomiting [14] presenting subsequently with Barrett's oesophagus [9,14], adenocarcinoma of the oesophagus [9–11] or proximal stomach [12], and squamous cell carcinoma of the oesophagus [13,14]. In a cohort of patients with anorexia nervosa ($n = 524$) diagnosed in north-east Scotland between 1965 and 1999, and followed up to mid-2002, one patient was reported to have died from oesophageal cancer, and one from adenocarcinoma without specification of primary site (from a total of 23 deaths) [15]. In a Danish cohort study including 2151 women hospitalised with anorexia nervosa during 1970–1993 with follow-up to 31st December 1996, one incident case of oesophageal cancer was observed compared to around 0.1 expected, yielding a non-significant standardised incidence ratio (SIR) of 20 (95% confidence interval 0.5–111) [16].

We conducted a population-based data linkage study, aiming to investigate the risk of oesophageal cancer among patients with a prior history of hospitalisation with eating disorder.

2. Methods

2.1. Study population and oversight

Eating disorders represent a spectrum of conditions with overlapping symptoms and behaviours [17]. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), which is used currently to code Scottish hospital and mortality records, identifies several categories of eating disorder, including anorexia nervosa (and atypical variant), bulimia nervosa (and atypical variant), and other eating disorders, including eating disorder unspecified [18]. Back-mapping to the ninth revision of the International Classification of Diseases (ICD-9) is imperfect – although there is a specific code for anorexia nervosa, bulimia nervosa has to be coded to a less specific category [19] (See Appendix).

In Scotland, a national linked database of general hospital discharge records, psychiatric hospital records, cancer registrations, and mortality records has been established by probability matching [20]. Estimates based on clerical checking suggest that rates of false positive and false negative linkages are maintained below 1% [21]. False positive and false negative links are likely to be less common nowadays because of more widespread availability and use of the Community Health Index (CHI) number, a unique national identifying number used in health service records in Scotland. We selected de-identified records of patients admitted for the first time to general or psychiatric hospitals between 1981 and 2011 with eating disorder as defined by any mention, in up to six discharge diagnosis fields, of the following diagnostic codes: ICD-9 307.1 and/or 307.5 (1981–March 1996); ICD-10 F50 (April 1996 onwards). When a patient had more than one relevant diagnostic code assigned, we based our selection on the earliest admission or, if there was more than one diagnosis during that first hospital episode, on the diagnosis recorded in the highest position on the discharge form. Since eating disorders are very rare in children younger than 10 or adults older than 60 years of age [22], the cohort was restricted to patients aged $\geq$10 years and $<$60 years at the date of first admission with eating disorder. This led to a potential study cohort of 4419 individuals.

In Scotland, although socio-economic deprivation has been associated with oesophageal cancer overall, the relationship appears to vary by histological sub-type [23]. Historically, eating disorders have been associated with high socio-economic status, although this relationship is not clear-cut, and an opposite relationship may apply to bulimia nervosa [24]. As an indicator of socio-economic position, based on postcode sectors of residence at the time of original diagnosis, individuals were assigned to population-weighted fifths of Carstairs deprivation scores by applying 1991 and 2001 census-derived Carstairs scores to the periods of diagnosis 1981–1995 and 1996–2011, respectively. The Carstairs deprivation index is based on small area of residence, and is derived from four variables collected at each decennial census: social class, unemployment, overcrowding, and car ownership [25].

The study was approved by the Privacy Advisory Committee of the National Health Service (NHS) National Services Scotland (NSS).

2.2. Outcome data

The incidence of oesophageal cancer (ICD-9 150; ICD-10 C15) was the main outcome of interest. Related outcomes included the incidence of oesophageal adenocarcinoma and oesophageal squamous cell carcinoma (both based on specific ICD-O morphology codes defined by the International Agency for Research on Cancer) [26], and the incidence of gastric cancer (ICD-9 151; ICD-10 C16) and cancer of the gastric cardia (ICD-9 151.0; ICD-10 C16.0), since there is the potential for misclassification of tumours arising in the vicinity of the oesophago-gastric junction.

In the absence of individual data on smoking and alcohol use in our study population, we sought to assess the potential confounding effect of these risk factors indirectly, by investigating additionally the incidence of lung cancer (ICD-9 162; ICD-10 C33-C34), first hospitalisation with chronic obstructive pulmonary disease (COPD: ICD-9 490–492, 496; ICD-10 J40–J44), and first hospitalisation associated with alcohol-related diagnoses (as defined in a previous publication [27]). See the Appendix for a full list of the diagnostic codes used to define eating disorders and outcomes.

2.3. Statistical analysis

Study subjects with any of these pre-specified outcomes (selected cancers, COPD, or alcohol-related diagnoses) prior to the date of their first recorded admission with eating disorder ($n = 410$; 9.3%) were excluded. In addition, to try and exclude patients with outcome-related symptoms, such as anorexia, that were originally misdiagnosed/misclassified/miscoded as eating disorders, we excluded the person-time and outcomes (cancers or hospitalisations) in the first year of follow-up after first hospital admission with eating disorder. This led to the exclusion of 322 persons (7.3%) who had a diagnosis of gastric cancer ($n = 2$), COPD ($n = 8$), alcohol-related conditions ($n = 266$), COPD and alcohol-related conditions ($n = 1$), or died ($n = 45$) within the first year of follow-up. Finally, 70 individuals were excluded because it was not possible to assign them to a deprivation category. After these exclusions, the study cohort included 3617 (82%) individuals. For the analysis of oesophageal, gastric and lung cancer incidence, follow-up was from 1 year after the earliest date of hospital admission with eating disorder to date of one of these incident cancers, date of death, or end of 2012, whichever occurred first. For the end-points of hospitalisation (COPD or alcohol-related), follow-up was from 1 year after the earliest date of hospital admission with eating disorder to date of first hospital admission (COPD or alcohol-related), date of death, or end of 2012, whichever occurred first.

Indirectly standardised incidence/hospitalisation ratios (SIRs/SHRs) and absolute excess risks (AERs) were calculated, using the general population as a reference group to generate expected

numbers of cases (based on age-, sex-, deprivation category-, and calendar period-specific rates of disease). Rates were calculated using decennial census-based, mid-year population estimates sourced from the General Register Office for Scotland (now part of National Records of Scotland). SIRs/SHRs were calculated as the ratio of observed to expected numbers of cases. AERs were calculated as the observed minus the expected number of cases divided by the number of person-years at risk and expressed as the rate per 10,000 person-years at risk. The AER reflects the additional absolute burden of disease beyond background rates. 95% confidence intervals for SIRs/SHRs and AERs were calculated by assuming that the observed numbers of events followed a Poisson distribution.

3. Results

3.1. Characteristics of the study population

The distribution and summary characteristics of the study population are shown in Table 1. Data are not shown separately for patients with bulimia nervosa ($n = 427$; 93% females) because it was only possible to identify such patients from April 1996 onwards, when ICD-10 replaced ICD-9 for classification and coding of hospital records in Scotland.

The majority of the cohort (90%) was female, and more than 75% had their first admission with eating disorder before the age of 30 years. Overall, there was a tendency for more patients to be assigned to the least deprived fifth (21%) compared with the most deprived fifth (19.2%) of the population, although this trend was reversed among patients with eating disorders other than anorexia nervosa, especially in those with bulimia nervosa (15.7% vs 22.5% – patients recorded from April 1996 onwards as explained above, underlying data available on request). Just over 60% of females were classified as having anorexia nervosa, compared with only 46% of males. The mean age at study entry was around 24 years, and the median calendar year at study entry was 1997. Patients were followed up for a median of 13.9 years (mean 14.5 years), corresponding to 52,455 person-years at risk. Seven oesophageal cancers were diagnosed during follow-up, all arising in females at a mean age of 55 years (range 35–72).

Table 2 shows the risks of the pre-specified outcomes, stratified by category of eating disorder.

Table 1
Distribution and summary characteristics of the study population.

	Males		Females		Persons	
	Number	%	Number	%	Number	%
Age-group (years) at first admission with eating disorder						
10–19	163	46.6	1346	41.2	1509	41.7
20–29	96	27.4	1183	36.2	1279	35.4
30–39	46	13.1	465	14.2	511	14.1
40–49	27	7.7	191	5.8	218	6.0
50–59	18	5.1	82	2.5	100	2.8
Deprivation fifth						
1 – Least deprived	73	20.9	687	21.0	760	21.0
2	67	19.1	686	21.0	753	20.8
3	68	19.4	669	20.5	737	20.4
4	64	18.3	608	18.6	672	18.6
5 – Most deprived	78	22.3	617	18.9	695	19.2
Type of eating disorder						
Anorexia nervosa (AN)	161	46.0	1977	60.5	2138	59.1
All eating disorders except AN	189	54.0	1290	39.5	1479	40.9
Total	350	9.7	3267	90.3	3617	100

	Males	Females	Persons
Mean age at study entry (years)	24.0	23.8	23.8
Median calendar year at study entry	1997	1997	1997
Median number of years of follow-up	14.0	13.9	13.9
Person-years at risk	5167	47,288	52,455
Number of oesophageal cancers diagnosed during follow-up	0	7	7
Mean age at diagnosis of oesophageal cancer	N/A	55.6	55.6

N/A: not applicable.

3.2. Risks of oesophageal and gastric cancer

Based on seven cases observed and 1.14 expected, the standardised incidence ratio (SIR) for oesophageal cancer in the entire cohort was 6.1 (95% confidence interval: 2.5–12.6), corresponding to an absolute excess risk of 1.1 per 10,000 person-years at risk (95% CI: 0.32–2.52). All of the oesophageal cancers were coded as squamous cell carcinoma, and all arose in women classified as having had anorexia nervosa. These seven individuals were first hospitalised with anorexia nervosa between 1981 and 1984 (although it is possible that some were admitted prior to the calendar period of the linked data available to us). They developed their oesophageal cancers between 2000 and 2011, after a mean interval of 22 years (range 19–28 years). The risks of gastric cancer and gastric cardia cancer were increased, but the estimates were very imprecise.

3.3. Risks of lung cancer, COPD, and alcohol-related conditions

The risk of lung cancer was increased slightly, but the confidence interval was wide. However, standardised hospitalisation ratios (SHRs) for COPD and especially for alcohol-related conditions were increased significantly across all categories of eating disorder, with a tendency to be higher in 'all eating disorders except anorexia nervosa'. SHRs were particularly increased in patients classified as bulimia nervosa: 4.1 (1.3–9.5) for COPD and 7.5 (5.7–9.7) for alcohol-related conditions (data not shown in Table 2, but available on request).

4. Discussion

We found a significant 6-fold increased risk of oesophageal cancer in this cohort of patients previously hospitalised with eating disorder. However, the confidence interval is wide, reflecting the relatively modest size of the study population, its relatively young age profile, limited duration of follow-up, and consequently the small number of oesophageal cancers diagnosed (also reflected by a low absolute excess risk).

Surveillance bias seems unlikely to explain our findings for two reasons. Firstly, oesophageal cancer is unlikely to remain undiagnosed for long, even in patients who are not in regular contact with health services. Indeed, it often results in death within less than a year of diagnosis. Secondly, although surveillance bias might be expected to exert its greatest impact during early years of follow-up, all of the cases of oesophageal cancer emerged at least 19 years after the first admission with eating disorder.

Even if our findings are valid, the relatively low lifetime prevalence of eating disorders [17] suggests that they are unlikely to contribute substantially to the population burden of oesophageal cancer. However, there is some evidence that the incidence of eating disorders is increasing over time [28], and it is still important for these patients and their clinicians to be aware that they may be at increased risk of oesophageal cancer later in life, with a view to achieving earlier investigation and diagnosis following the onset of any relevant symptoms or signs.

Table 2
Risks (standardised incidence/hospitalisation ratios and absolute excess risks) of selected outcomes by category of eating disorder.[a]

Outcome	Observed number of events (O)	Person years at risk (PYAR)	Expected number of events (E)	Standardised incidence/ hospitalisation ratio (SIR/SHR)[a]	95% confidence interval		Absolute excess risk (AER) per 10,000 PYAR	95% Confidence interval	
					Lower	Upper		Lower	Upper
All eating disorders combined									
Oesophageal cancer	7	52,455	1.14	6.12	2.46	12.60	1.12	0.32	2.52
Adenocarcinoma	0	52,462	0.46	0.00	0.00	8.02	N/A	N/A	N/A
Squamous cell carcinoma	7	52,455	0.57	12.21	4.91	25.15	1.23	0.42	2.62
Gastric cancer	3	52,457	1.50	2.00	0.41	5.84	0.29	−0.17	1.38
Gastric cardia cancer	1	52,461	0.31	3.19	0.08	17.77	0.13	−0.05	0.99
Lung cancer	11	52,454	8.93	1.23	0.62	2.20	0.39	−0.65	2.04
COPD hospital admission	61	52,190	31.61	1.93	1.48	2.48	5.63	2.91	8.96
Alcohol-related hospital admission	412	48,743	112.31	3.67	3.32	4.04	61.48	53.46	70.05
Anorexia nervosa (AN)									
Oesophageal cancer	7	35,919	0.70	9.96	4.00	20.51	1.75	0.58	3.80
Adenocarcinoma	0	35,926	0.27	0.00	0.00	13.66	N/A	N/A	N/A
Squamous cell carcinoma	7	35,919	0.37	19.06	7.66	39.27	1.85	0.69	3.94
Gastric cancer	1	35,924	0.98	1.02	0.03	5.69	0.01	−0.26	1.28
Gastric cardia cancer	0	35,926	0.19	0.00	0.00	19.42	N/A	N/A	N/A
Lung cancer	7	35,919	5.76	1.22	0.49	2.51	0.35	−0.82	2.42
COPD hospital admission	32	35,795	20.96	1.53	1.04	2.16	3.08	0.23	6.79
Alcohol-related hospital admission	230	33,650	74.26	3.10	2.71	3.52	46.28	37.74	55.61
All eating disorders except AN									
Oesophageal cancer	0	16,536	0.44	0	0.00	8.38	N/A	N/A	N/A
Adenocarcinoma	0	16,536	0.19	0	0.00	19.42	N/A	N/A	N/A
Squamous cell carcinoma	0	16,536	0.21	0	0.00	17.57	N/A	N/A	N/A
Gastric cancer	2	16,533	0.52	3.84	0.46	13.87	0.90	−0.17	4.05
Gastric cardia cancer	1	16,535	0.12	8.31	0.21	46.30	0.53	−0.06	3.29
Lung cancer	4	16,535	3.17	1.26	0.34	3.23	0.50	−1.27	4.28
COPD hospital admission	29	16,395	10.65	2.72	1.82	3.91	11.19	5.33	18.90
Alcohol-related hospital admission	182	15,094	38.05	4.78	4.11	5.53	95.37	78.40	114.20

N/A: not applicable.
[a] Indirectly standardised for age, sex, calendar period of follow-up, and deprivation.

Our data do not support the hypothesis that patients with eating disorders are at higher than expected risk of oesophageal adenocarcinoma caused by self-induced vomiting practiced as a method of weight control. None of the cancers diagnosed were classified as adenocarcinomas. Furthermore, the risk of oesophageal cancer was confined to women with a history of anorexia nervosa who may be less inclined to indulge in self-induced vomiting [2]. However, it may be premature to rule out an increased risk of oesophageal adenocarcinoma entirely, in the face of limited statistical power.

It is also worth considering the possibility that self-induced vomiting could cause chronic physical damage to oesophageal mucosa through repeated microtrauma, rather than chemical damage caused by gastric acid. For example, another type of physical damage, thermal injury, has been associated with subsequent increased risk of oesophageal cancer (and specifically squamous cell carcinoma [29]) in some studies [30].

However, the most likely explanation for our findings would seem to be confounding by the main established risk factors for oesophageal squamous cell carcinoma, namely tobacco and alcohol, perhaps compounded by chronic nutritional deficiency [6]. Malnutrition and insufficient intake of micronutrients certainly occur in people with eating disorders [7], but despite evidence of alterations in cell-mediated immunity, adaptation processes seem to occur enabling immune function to be preserved during long periods of the illness [31]. Nevertheless, there is evidence that nutritional deficiency is positively associated with oesophageal cancer [6], and it is conceivable that prolonged periods of nutritional deficiency could increase susceptibility to other carcinogenic risk factors, such as tobacco and alcohol.

As noted previously, patients with eating disorders seem to be susceptible to smoking [3] and alcohol use disorders [4,5], and this also seems to be borne out by our analysis of hospitalisation for relevant associated conditions (COPD and alcohol-related conditions). The fact that smoking and alcohol use disorders seem to be more common in patients with eating disorders with features other than restrictive anorexia nervosa [3,5] (also borne out, to some extent, by our results), is not really consistent with our finding that the oesophageal cancers were restricted to patients with anorexia nervosa. However, this may simply be a reflection of the smaller number of patients classified with eating disorders other than anorexia nervosa. Moreover, it is important to remember that there is considerable overlap of characteristics between various types of eating disorders [17]. For example, the ICD-10 definition of bulimia nervosa (F50.2) states that "There is often, but not always, a history of an earlier episode of anorexia nervosa, the interval ranging from a few months to several years" [18]. Against this background, it is also important to remember that we assigned the diagnosis of eating disorder based on the

earliest admission or, if there was more than one diagnosis during that first hospital episode, on the diagnosis recorded in the highest position. At the same time, it may be unrealistic to expect hospital administrative data collected routinely and coded to successive editions of the International Classification of Diseases to capture the intricacies of the various sub-categories of eating disorders, which have themselves altered over time.

In a Swedish cohort study of 6009 women hospitalised with anorexia nervosa between 1973 and 2003 with follow-up to 31st December 2003, the SIR for cancer of digestive organs was 1.4 (0.6–2.7) based on eight cases [32]. A further breakdown of these cases was not provided on the grounds of inadequate statistical power. While these results do not support our main finding, it is possible that they could conceal an excess risk of oesophageal cancer if there was a deficit of other digestive tract cancers. For example, the Danish cohort study mentioned previously [16] reported a very similar SIR for cancer of digestive organs (SIR 1.3, 0.3–3.9) based on three cases, although none of these was a colorectal cancer, perhaps reflecting higher than average rates of physical activity among patients with eating disorders [33]. While the risk of oesophageal cancer was spectacularly high (SIR 20), it was based on just a single case, with a very wide 95% confidence interval (0.5–111). It may be that there is greater scope to detect an excess risk in Scotland, where the world age-standardised incidence rate of oesophageal cancer among women was 4.6 per 100,000 during 2003–2007 compared with 2.1 in Denmark and 1.0 in Sweden [34].

Like previous cohort studies in Denmark [16] and Sweden [32], our study can be regarded as population-based in the sense that the data cover all publically provided healthcare, and private provision of mental health services in Scotland is negligible. However, by restricting our study to hospitalised patients, who are likely to occupy the more severe end of the eating disorders spectrum, we may have over-estimated the relative risk of oesophageal cancer associated with eating disorders.

In Scotland, general hospitalisation data are supported by an active programme of quality assurance including regular assessments of data quality. In relation to discharges from general hospitals, the accuracy of coding of main diagnosis has been estimated to be around 88% overall and has been relatively stable for at least 20 years [35]. Less evidence is available on which to base an assessment of the quality of psychiatric hospital data. However, as noted previously, many features of our study population seem to be consistent with those reported from more detailed, albeit smaller studies of patients with various categories of eating disorders [3–5,17,24].

Based on routinely available indicators [34], and specific studies of completeness of case ascertainment [36] and data reliability (including the coding of tumour morphology) [37], the quality of cancer registration data in Scotland is believed to be comparatively high. There is corroborating evidence for the registered oesophageal cancers included in our study in the sense that all the patients are deceased and have their underlying cause of death also coded as oesophageal cancer.

A further strength of our study was the ability to standardise for socio-economic deprivation, which has been associated both with eating disorders [24] and oesophageal cancer [23] in some studies. However, it must be acknowledged that our indicator of deprivation has limitations because it refers to a single point in time, is based on area of residence rather than individual characteristics, and is based on census data that are only updated every 10 years.

As pointed out previously, and in common with other studies, the two main weaknesses of our study are limited statistical power, and a lack of information on potential confounding factors at individual level. A further weakness is that, particularly for patients hospitalised with eating disorders in the early 1980s, we may not have identified the earliest date of hospitalisation because the linked data available to us did not extend back before 1981. As a result, we may have under-estimated person-years at risk and therefore expected numbers of cases, leading to an over-estimation of risk. However, the impact of this potential artefact seems likely to be small because the missing person-years are likely to be concentrated at the younger end of the age range, when the risk of oesophageal cancer is very low. Even in the data available to us, we found that the expected number of oesophageal cancers was very low during early years of follow-up (0.06 up to <10 years after admission with eating disorder). Lastly, another minor weakness is that we were not able to identify emigrants from Scotland who will have been lost to follow-up.

In summary, our results suggest that women with a past history of eating disorder (specifically anorexia nervosa) are at increased risk of squamous cell carcinoma of the oesophagus. This may be explained by concomitant alcohol use disorder and smoking, possibly aggravated by nutritional deficiencies. Our data do not support the hypothesis that patients with eating disorders are at higher than expected risk of oesophageal adenocarcinoma caused by self-induced vomiting practiced as a method of weight control. Our findings need to be replicated, ideally in a larger study population with longer follow-up and information on potential confounding factors at an individual level. In the meantime, irrespective of causal mechanisms, it may be sensible for physicians to exercise a high index of suspicion in patients with a past history of eating disorder who present with symptoms that might suggest a diagnosis of oesophageal cancer.

Conflict of interest statement

None of the authors have any relevant conflicts of interest to declare in relation to this manuscript.

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Authorship contributions

The author contributions were as follows: David Brewster had the idea for the study, developed the study protocol, analysis plan and grant application, obtained funding and permission for the study, interpreted the data, and drafted, revised and submitted the manuscript. Siân Nowell analysed the data, and reviewed the manuscript. David Clark supervised the analysis of data and reviewed the manuscript. None of the authors have any relevant conflicts of interest.

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Appendix. Diagnostic codes used to identify 'exposure' (eating disorders) and outcomes

All eating disorders combined

ICD-9 307.1, 307.5; ICD-10 F50

Anorexia nervosa (AN)

ICD-9 307.1; ICD-10 F50.0, F50.1

All eating disorders except AN

ICD-9 307.5; ICD-10 F50.2, F50.3, F50.4, F50.5, F50.8, F50.9

Bulimia nervosa (BN)

ICD-10 F50.2, F50.3

ICD-9 code	Diagnostic term	ICD-10 code	Diagnostic term
307.1	Anorexia nervosa	F50.0	Anorexia nervosa
307.5	Other and unspecified disorders of eating	F50.1	Atypical anorexia nervosa
		F50.2	Bulimia nervosa
		F50.3	Atypical bulimia nervosa
		F50.4	Overeating associated with other psychological disorders
		F50.5	Vomiting associated with other psychological disturbances
		F50.8	Other eating disorders
		F50.9	Eating disorder, unspecified

Oesophageal cancer (main outcome)

ICD-9 150; ICD-10 C15

Oesophageal adenocarcinoma

ICD-9 150; ICD-10 C15 in conjunction with ICD-O morphology codes 8140–8141, 8143–8145, 8190–8231, 8260–8263, 8310, 8401, 8480–8490, 8550–8551, 8570–8574, 8576

Oesophageal squamous cell carcinoma

ICD-9 150; ICD-10 C15 in conjunction with ICD-O morphology codes 8050–8078, 8083–8084

Gastric cancer

ICD-9 151; ICD-10 C16

Gastric cardia cancer

ICD-9 151.0; ICD-10 C16.0

Lung cancer

ICD-9 162; ICD-10 C33-C34

Chronic obstructive pulmonary disease (COPD)

ICD-9 code	ICD-10 code	Condition
490	J40	Bronchitis, not specified as acute or chronic
	J41	Simple and mucopurulent chronic bronchitis
491	J42	Unspecified chronic bronchitis
492	J43	Emphysema
496	J44	Other chronic obstructive pulmonary disease

Alcohol-related diagnoses

ICD-9 code	ICD-10 code	Condition
	E244	Alcohol induced Pseudo-Cushing's syndrome
	E512	Wernicke's encephalopathy
291	F10	Mental and behavioural disorders due to use of alcohol
303		
	G312	Degeneration of nervous system due to alcohol
3575	G621	Alcoholic polyneuropathy
	G721	Alcoholic myopathy
4255	I426	Alcoholic cardiomyopathy
5353	K292	Alcoholic gastritis
5710	K70	Alcoholic liver disease
5711		
5712		
5713		
	K860	Alcohol-induced chronic pancreatitis
	O354	Maternal care for (suspected) damage to foetus from alcohol
7903	R780	Finding of alcohol in blood
9800	T510	Toxic effect of ethanol
9801	T511	Toxic effect of methanol
3050	T519	Toxic effect of alcohol, unspecified
9809		
E860	X45	Accidental poisoning by and exposure to alcohol
	X65	Intentional self-poisoning by and exposure to alcohol
	Y15	Poisoning by and exposure to alcohol undetermined intent
E9473	Y573	Alcohol deterrents
	Y90	Evidence of alcohol involvement determined by blood alcohol level
	Y91	Evidence of alcohol involvement determined by level intoxication
	Z502	Alcohol rehabilitation
	Z714	Alcohol abuse counselling and surveillance
	Z721	Alcohol use

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